PATENT COOPERATION TREATY

PCT

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

(PCT Article 36 and Rule 70)

Applicant's or agent's file reference RE/PG4773	FOR FURTHER ACTION	See Notification of Transmittal of International Preliminary Examination Report (Form PCT/IPEA/416)
International application No. PCT/EP 03/02878	International filing date *(day/month/year)* 18.03.2003	Priority date *(day/month/year)* 19.03.2002
International Patent Classification (IPC) or both national classification and IPC A61K39/39		
Applicant GLAXO GROUP LIMTED et al.		

1. This international preliminary examination report has been prepared by this International Preliminary Examining Authority and is transmitted to the applicant according to Article 36.

2. This REPORT consists of a total of 6 sheets, including this cover sheet.

   ☒ This report is also accompanied by ANNEXES, i.e. sheets of the description, claims and/or drawings which have been amended and are the basis for this report and/or sheets containing rectifications made before this Authority (see Rule 70.16 and Section 607 of the Administrative Instructions under the PCT).

   These annexes consist of a total of 7 sheets.

3. This report contains indications relating to the following items:

   - I ☒ Basis of the opinion
   - II ☐ Priority
   - III ☒ Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
   - IV ☐ Lack of unity of invention
   - V ☒ Reasoned statement under Rule 66.2(a)(ii) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
   - VI ☐ Certain documents cited
   - VII ☐ Certain defects in the international application
   - VIII ☐ Certain observations on the international application

Date of submission of the demand	Date of completion of this report
06.10.2003	22.03.2004
Name and mailing address of the international preliminary examining authority: European Patent Office D-80298 Munich Tel. +49 89 2399 - 0 Tx: 523656 epmu d Fax: +49 89 2399 - 4465	Authorized Officer Pinheiro Vieira, E Telephone No. +49 89 2399-7865

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

International application No. PCT/EP 03/02878

I. Basis of the report

1. With regard to the **elements** of the international application *(Replacement sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to this report since they do not contain amendments (Rules 70.16 and 70.17))*:

Description, Pages

1-27 as originally filed

Claims, Numbers

1-8 received on 27.02.2004 with letter of 26.02.2004

Drawings, Sheets

1/3-3/3 as originally filed

2. With regard to the **language**, all the elements marked above were available or furnished to this Authority in the language in which the international application was filed, unless otherwise indicated under this item.

These elements were available or furnished to this Authority in the following language: , which is:

- ☐ the language of a translation furnished for the purposes of the international search (under Rule 23.1(b)).
- ☐ the language of publication of the international application (under Rule 48.3(b)).
- ☐ the language of a translation furnished for the purposes of international preliminary examination (under Rule 55.2 and/or 55.3).

3. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application, the international preliminary examination was carried out on the basis of the sequence listing:

- ☐ contained in the international application in written form.
- ☐ filed together with the international application in computer readable form.
- ☐ furnished subsequently to this Authority in written form.
- ☐ furnished subsequently to this Authority in computer readable form.
- ☐ The statement that the subsequently furnished written sequence listing does not go beyond the disclosure in the international application as filed has been furnished.
- ☐ The statement that the information recorded in computer readable form is identical to the written sequence listing has been furnished.

4. The amendments have resulted in the cancellation of:

- ☐ the description, pages:
- ☐ the claims, Nos.:
- ☐ the drawings, sheets:

5. ☐ This report has been established as if (some of) the amendments had not been made, since they have been considered to go beyond the disclosure as filed (Rule 70.2(c)).

   (Any replacement sheet containing such amendments must be referred to under item 1 and annexed to this report.)

6. Additional observations, if necessary:

III. Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

1. The questions whether the claimed invention appears to be novel, to involve an inventive step (to be non-obvious), or to be industrially applicable have not been examined in respect of:

   ☐ the entire international application,

   ☒ claims Nos. 1-4,7,8

   because:

   ☒ the said international application, or the said claims Nos. 1-4,7,8 relate to the following subject matter which does not require an international preliminary examination (specify):

   see separate sheet

   ☐ the description, claims or drawings *(indicate particular elements below)* or said claims Nos. are so unclear that no meaningful opinion could be formed *(specify)*:

   ☐ the claims, or said claims Nos. are so inadequately supported by the description that no meaningful opinion could be formed.

   ☐ no international search report has been established for the said claims Nos.

2. A meaningful international preliminary examination cannot be carried out due to the failure of the nucleotide and/or amino acid sequence listing to comply with the standard provided for in Annex C of the Administrative Instructions:

   ☐ the written form has not been furnished or does not comply with the Standard.

   ☐ the computer readable form has not been furnished or does not comply with the Standard.

V. Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Yes:	Claims	6
	No:	Claims	5
Inventive step (IS)	Yes:	Claims	6
	No:	Claims	5
Industrial applicability (IA)	Yes:	Claims	5,6
	No:	Claims	

2. Citations and explanations

see separate sheet

III.1 Claims 1-4, 7 and 8 relate to subject-matter considered by this Authority to be covered by the provisions of Rule 67.1(iv) PCT. Consequently, no opinion will be formulated with respect to the industrial applicability of the subject-matter of these claims (Article 34(4)(a)(i) PCT).

V.1 The amendments filed with the letter dated 26.02.2004 comply with the requirements of Article 34(2)(b) PCT.

V.2 Novelty and inventive step (Art. 33 PCT).

2.1 Reference is made to the following documents:

D1 = US6083505
D2 = Bernstein et al; vol. 167, no. 3, 1993, pages 731-735
D3 = Harrison et al; vol. 19, no. 13-14, 2001, pages 1820-1826
D4 = Vasilakos et al; vol. 204, no. 1, 2000, pages 64-74
D5 = WO0047719

2.2 The application concerns a method of vaccinating an individual comprising vaccinating the individual with a first vaccine composition on one or more occasions comprising a nucleic acid encoding a protein or polypeptide but not an imidazo(4,5-c)quinolin-4-amine derivative, and vaccinating again the same individual by another vaccine composition which comprises the same nucleic acid and imidazo(4,5-c)quinolin-4-amine derivative.

D1 (columns 3 and 9; examples; claims) discloses a method of vaccinating an individual comprising administering sequentially or simultaneously an imidazo(4,5-c)quinolin-4-amine derivative and an immunogen component.

D2 (abstract; figure 1; discussion) discloses a vaccine comprising imiquimod and a type 2 glycoprotein.

D3 (abstract; experimental design; results) discloses an immune modulator, imiquimod, given alone or in combination with an HSV vaccine and its effect on HSV immune responses.

D4 (abstract; figures 1-6; materials and methods) discloses the effects of

imidazoquinolines as vaccine adjuvants, given alone or in combination with an antigen.

D5 (pages 2 and 3; examples) concerns the stimulation of immature dendritic cells by an imidazoquinoline derivative with formulas I-IX(b) and their use (page 23).

2.3 Given that the above mentioned documents neither discloses nor suggests a kit comprising a first and a second vaccine composition comprising the same **nucleic acid** characterized in that only the second vaccine composition comprises an imidazo(4,5-c)quinolin-4-amine derivative, the subject matter in claim 6 is novel and appears to be inventive (the Applicant is reminded that the intermediate document WO0224225 appears to be novelty destroying for this claim).
Claim 5 is not novel as a vaccine administration device is disclosed in every prior art documents D1-D5 (see item 3.2 below).

V.3 Other objections.

3.1 The Applicant's attention is drawn to document WO0224225, cited as an intermediate document, as it appears to be novelty destroying for claims 1-8.

3.2 The Applicant's attention is drawn to the fact that **claim 5** does not contain any features that characterize the claimed device as such, it rather describes the components that are used with the device than the device per se. Therefore, the subject matter in claim 5 does not comply with the requirements of Art. 6 PCT.

3.3 In claim 8, formula (II), the variable "**n**" and a bond linking N to R_{12} are missing from the drawings. In the same claim there is a reference in the text to a substituent "$\mathbf{R_5}$" in formula (III) but this substituent is absent from said formula. For the sake of clarity (Art. 6 PCT) said inconsistencies should be removed. The Applicant should take great care not to introduce subject-matter which extends beyond the content of the application as filed, contrary to Article 34(2)(b) PCT.

3.4 The expression "substantially simultaneously" in claim 7 renders the subject matter of said claim unclear (Art. 6 PCT).

PG4773 Amended Claims during PCT International Phase

1. A method of vaccinating an individual comprising the steps of:

(a) vaccinating the individual with a first vaccine composition on one or more occasions, characterised in that said vaccine comprises an antigen but does not comprise an imidazo [4,5-c] quinolin – 4 – amine derivative, and

(b) after waiting an appropriate length of time, vaccinating the same individual one of more times with a second vaccine, characterised in that the second vaccine composition comprises the same antigen as the first vaccine, the second vaccine being administered with an imidazo [4,5-c] quinolin – 4 – amine derivative, wherein the said antigen is a nucleic acid encoding a protein or polypeptide.

2. The method of vaccinating an individual as claimed in claim 1 further comprising a repeat of step (a) after step (b).

3. The method of vaccinating an individual as claimed in claim 1 wherein the second vaccine composition comprising the imidazo [4,5-c] quinolin – 4 – amine derivative is the final vaccine dose administered.

4. Use of an imidazo [4,5-c] quinolin – 4 – amine derivative and an antigen in the manufacture of a booster dose of a vaccine medicament for administration to an individual, characterised in that the individual previously received a priming dose of the vaccine medicament comprising the same antigen but which did not comprise an imidazo [4,5-c] quinolin – 4 – amine derivative, wherein the said antigen is a nucleic acid encoding a protein or polypeptide.

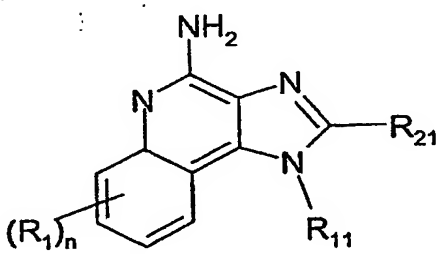
5. A vaccine administration device comprising and antigen and an imidazo [4,5-c] quinolin – 4 – amine derivative, the device being packaged together with an instruction leaflet advising that the administration device is used to administer the vaccine composition only to individuals that had previously received a vaccine comprising the same antigen but which did not comprise an imidazo [4,5-c] quinolin – 4 – amine derivative, wherein the said antigen is a nucleic acid encoding a protein or polypeptide.

6. A kit comprising a first vaccine composition and a second vaccine composition, wherein the first vaccine composition and the second composition contain the same antigen characterised in that the first vaccine composition does not comprise an imidazo [4,5-c] quinolin – 4 – amine derivative, and the second vaccine composition

comprises an imidazo [4,5-c] quinolin – 4 – amine derivative, wherein the said antigen is a nucleic acid encoding a protein or polypeptide.

7. A method as claimed in claim 1 wherein the antigen and imidazo [4,5-c] quinolin – 4 – amine derivative are administered substantially simultaneously.

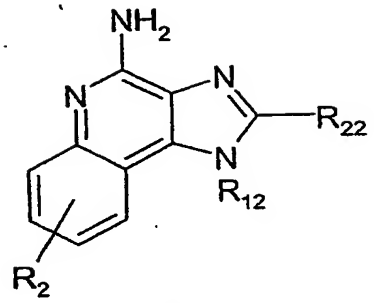
8. A method according to claim 1 or 2 wherein the 1H-imidazo[4,5-c]quinolin-4-amine derivative is a compound defined by one of formulae I-VI:



(I)

wherein

R_{11} is selected from the group consisting of straight or branched chain alkyl, hydroxyalkyl, acyloxyalkyl, benzyl, (phenyl)ethyl and phenyl, said benzyl, (phenyl)ethyl or phenyl substituent being optionally substituted on the benzene ring by one or two moieties independently selected from the group consisting of alkyl of one to about four carbon atoms, alkoxy of one to about four carbon atoms and halogen, with the proviso that if said benzene ring is substituted by two of said moieties, then said moieties together contain no more than 6 carbon atoms; R_{21} is selected from the group consisting of hydrogen, alkyl of one to about eight carbon atoms, benzyl, (phenyl)ethyl and phenyl, the benzyl, (phenyl)ethyl or phenyl substituent being optionally substituted on the benzene ring by one or two moieties independently selected from the group consisting of alkyl of one to about four carbon atoms, alkoxy of one to about four carbon atoms and halogen, with the proviso that when the benzene ring is substituted by two of said moieties, then the moieties together contain no more than 6 carbon atoms; and each R_1 is independently selected from the group consisting of hydrogen, alkoxy of one to about four carbon atoms, halogen and alkyl of one to about four carbon atoms, and n is an integer from 0 to 2, with the proviso that if n is 2, then said R_{11} groups together contain no more than 6 carbon atoms;

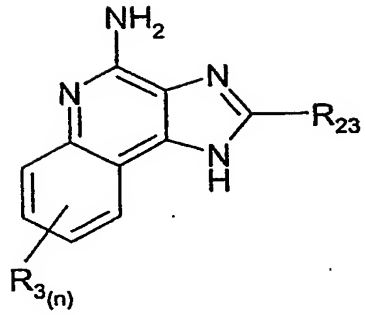


(II)

wherein

R_{12} is selected from the group consisting of straight chain or branched chain alkenyl containing 2 to about 10 carbon atoms and substituted straight chain or branched chain alkenyl containing 2 to about 10 carbon atoms, wherein the substituent is selected from the group consisting of straight chain or branched chain alkyl containing 1 to about 4 carbon atoms and

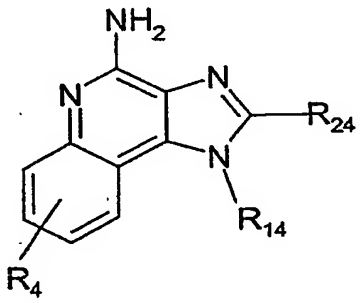
cycloalkyl containing 3 to about 6 carbon atoms; and cycloalkyl containing 3 to about 6 carbon atoms substituted by straight chain or branched chain alkyl containing 1 to about 4 carbon atoms; and R_{22} is selected from the group consisting of hydrogen, straight chain or branched chain alkyl containing one to about eight carbon atoms, benzyl, (phenyl)ethyl and phenyl, the benzyl, (phenyl)ethyl or phenyl substituent being optionally substituted on the benzene ring by one or two moieties independently selected from the group consisting of straight chain or branched chain alkyl containing one to about four carbon atoms, straight chain or branched chain alkoxy containing one to about four carbon atoms, and halogen, with the proviso that when the benzene ring is substituted by two such moieties, then the moieties together contain no more than 6 carbon atoms; and each R_2 is independently selected from the group consisting of straight chain or branched chain alkoxy containing one to about four carbon atoms, halogen, and straight chain or branched chain alkyl containing one to about four carbon atoms, and n is an integer from zero to 2, with the proviso that if n is 2, then said R_2 groups together contain no more than 6 carbon atoms;



(III)

wherein

R_{23} is selected from the group consisting of hydrogen, straight chain or branched chain alkyl of one to about eight carbon atoms, benzyl, (phenyl)ethyl and phenyl, the benzyl, (phenyl)ethyl or phenyl substituent being optionally substituted on the benzene ring by one or two moieties independently selected from the group consisting of straight chain or branched chain alkyl of one to about four carbon atoms, straight chain or branched chain alkoxy of one to about four carbon atoms, and halogen, with the proviso that when the benzene ring is substituted by two such moieties, then the moieties together- contain no more than 6 carbon atoms; and each R_5 is independently selected from the group consisting of straight chain or branched chain alkoxy of one to about four-carbon atoms, halogen, and 30 straight chain or branched chain alkyl of one to about four carbon atoms, and n is an integer from zero to 2, with the proviso that if n is 2, then said R_3 groups together contain no more than 6 carbon atoms;

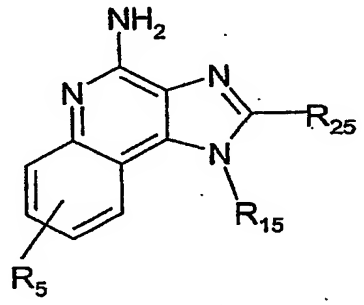


(IV)

wherein

R_{14} is $-CHR_AR_B$ wherein R_B is hydrogen or a carbon-carbon bond, with the proviso that when R_B is hydrogen R_A is alkoxy of one to about four carbon atoms,

hydroxyalkoxy of one to about four carbon atoms, 1-alkynyl of two to about ten carbon atoms, tetrahydropyranyl, alkoxyalkyl wherein the alkoxy moiety contains one to about four carbon atoms and the alkyl moiety contains one to about four carbon atoms, 2-, 3-, or 4-pyridyl, and with the further proviso that when R_B is a carbon-carbon bond R_B and R_A together form a tetrahydrofuranyl group optionally substituted with one or more substituents independently selected from the group consisting of hydroxy and hydroxyalkyl of one to about four carbon atoms; R_{24} is selected from the group consisting of hydrogen, alkyl of one to about four carbon atoms, phenyl, and substituted phenyl wherein the substituent is selected from the group consisting of alkyl of one to about four carbon atoms, alkoxy of one to about four carbon atoms, and halogen; and R_4 is selected from the group consisting of hydrogen, straight chain or branched chain alkoxy containing one to about four carbon atoms, halogen, and straight chain or branched chain alkyl containing one to about four carbon atoms;

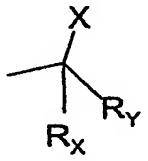


(V)

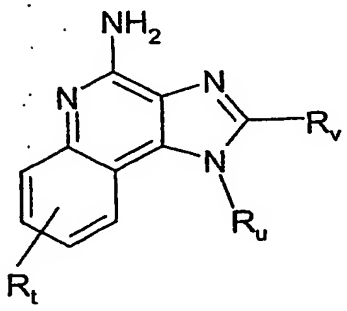
wherein

R_{15} is selected from the group consisting of: hydrogen; straight chain or branched chain alkyl containing one to about ten carbon atoms and substituted straight chain or branched chain alkyl containing one to about ten carbon atoms, wherein the substituent is selected from the group consisting of cycloalkyl containing three to about six carbon atoms and cycloalkyl containing three to about six carbon atoms substituted by straight chain or branched chain alkyl containing one to about four carbon atoms; straight chain or branched chain alkenyl containing two to about ten carbon atoms and substituted straight chain or branched chain alkenyl containing two to about ten carbon atoms, wherein the substituent is selected from the group consisting of cycloalkyl containing three to about six carbon atoms and cycloalkyl containing three to about six carbon atoms substituted by straight chain or branched chain alkyl containing one to about four carbon atoms; hydroxyalkyl of

one to about six carbon atoms; alkoxyalkyl wherein the alkoxy moiety contains one to about four carbon atoms and the alkyl moiety contains one to about six carbon atoms; acyloxyalkyl wherein the acyloxy moiety is alkanoyloxy of two to about four carbon atoms or benzoyloxy, and the alkyl moiety contains one to about six carbon atoms; benzyl; (phenyl)ethyl; and phenyl; said benzyl, (phenyl)ethyl or phenyl substituent being optionally substituted on the benzene ring by one or two moieties independently selected from the group consisting of
alkyl of one to about four carbon atoms, alkoxy of one to about four carbon atoms, and halogen, with the proviso that when said benzene ring is substituted by two of said moieties, then the moieties together contain no more than six carbon atoms;
R_{25} is



wherein
R_X and R_Y are independently selected from the group consisting of hydrogen, alkyl of one to about four carbon atoms, phenyl, and substituted phenyl wherein the substituent is elected from the group consisting of alkyl of one to about four carbon atoms, alkoxy of one to about four carbon atoms, and halogen; X is selected from the group consisting of alkoxy containing one to about four carbon atoms, alkoxyalkyl wherein the alkoxy moiety contains one to about four carbon atoms and the alkyl moiety contains one to about four carbon atoms, haloalkyl of one to about four carbon atoms, alkylamido wherein the alkyl group contains one to about four carbon atoms, amino, substituted amino wherein the substituent is alkyl or hydroxyalkyl of one to about four carbon atoms, azido, alkylthio of one to about four carbon atoms; and R_5 is selected from the group consisting of hydrogen, straight chain or branched chain alkoxy containing one to about four carbon atoms, halogen, and straight chain or branched chain alkyl containing one to about four carbon atoms;



VI

Wherein

R_t is selected from the group consisting of hydrogen, straight chain or branched chain alkoxy containing one to about four carbon atoms, halogen, and straight chain or branched chain alkyl containing one to about four carbon atoms;

R_u is 2-methylpropyl or 2-hydroxy-2-methylpropyl; and

R_v is hydrogen, alkyl of one to about six carbon atoms, or alkoxyalkyl wherein the alkoxy moiety contains one to about four carbon atoms and the alkyl moiety contains one to about four carbon atoms.

or a pharmaceutically acceptable salt of any of the foregoing